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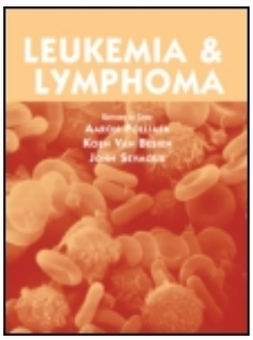

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ORIGINAL ARTICLE: CLINICAL

Brentuximab vedotin (SGN-35) in patients with transplant-naive relapsed/refractory Hodgkin lymphoma

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Abstract

Only limited data are available on the role of brentuximab vedotin (SGN-35) in transplant-naive relapsed or refractory patients with Hodgkin lymphoma (HL). We thus retrospectively analyzed 14 patients with primary refractory or relapsed HL who were treated with brentuximab vedotin as single agent in a named patient program, who had not received prior high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) due to refractory disease ($n = 9$), comorbidity ($n = 4$) and unknown reasons ($n = 1$). Brentuximab vedotin resulted in an overall response rate of 71% (10/14) with five complete responses (CRs). Five of those patients with refractory disease and four patients with relevant comorbidity responded. Consolidating ASCT ($n = 4$) or allogeneic SCT ($n = 1$) was performed in five patients. Median progression-free survival (PFS) was 9 months and the median overall survival (OS) was not reached. These data indicate the therapeutic efficacy of brentuximab vedotin in chemotherapy-refractory transplant-naive patients with HL.

Keywords: Brentuximab vedotin, Hodgkin lymphoma, no prior ASCT

Introduction

In contrast to the results achieved with first-line treatment [1,2], the prognosis of patients with Hodgkin lymphoma (HL) with relapsed disease is significantly poorer, with about 50% achieving long-term remission when treated with high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) [3,4]. In particular, those with refractory disease and older patients with relapsed HL have a dismal prognosis [5–7]. Since sensitivity to second-line induction therapy has been identified as a predictive marker for outcome after ASCT, even patients with primary progressive disease can benefit from HDCT [8]. An effective reinduction therapy for those suffering from primary progressive and chemotherapy-refractory HL should include a non-cross-resistant drug. Since HDCT is associated with significant morbidity and mortality in older patients with relapsed HL, new treatment approaches are also warranted in this group [5]. Thus, the availability of a new, better-tolerated and effective reinduction therapy is of key interest, especially for those with refractory HL and for older patients with relapsed HL.

Brentuximab vedotin (SGN-35) is a new antibody–drug conjugate (ADC) which consists of a chimeric anti-CD30 antibody conjugated to four molecules of the synthetic antitubulin chemotherapeutic agent, monomethyl auristatin E (MMAE) [9]. CD30 is abundant on the cell surface of the malignant cells in HL as well as anaplastic large cell lymphoma (ALCL) [10,11]. Brentuximab vedotin has shown impressive anti-tumor efficacy in patients with relapsed HL [8,11]. In the pivotal phase II trial including 102 heavily pretreated patients with HL, the overall response rate (ORR) was 75% with a median duration of 5.6 months. Importantly, 34% achieved a complete remission (CR) with a median response duration of 20.5 months [12].

Based on these excellent clinical data, the US Food and Drug Administration (FDA) approved brentuximab vedotin for the treatment of patients with HL who have either failed ASCT or had at least two prior multi-agent chemotherapy regimens and who are not candidates for ASCT.

Since there is very limited experience with brentuximab vedotin in those patients with HL who fail to achieve a remission before HDCT and in older patients with HL who are ineligible for HDCT, we retrospectively analyzed 14 patients with HL who were treated with brentuximab vedotin within

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There is an accompanying commentary that discusses this paper. Please refer to the issue Table of Contents.

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a named patient program (NPP) and who did not receive HDCT and ASCT prior to brentuximab vedotin treatment.

Materials and methods

Since March 2010, the German Hodgkin Study Group (GHSG) and associated centers have treated patients with histologically confirmed refractory or relapsed HL within a NPP initiated by the companies responsible for brentuximab vedotin (Seattle Genetics, Millennium, Takeda). All participants gave written informed consent. The main inclusion criterion was a normal organ function including peripheral blood counts within the normal range. Patients received a 30 min infusion of brentuximab vedotin dosed at 1.8 mg/kg body weight every 3 weeks. No pre-medication was administered. Toxic events were assessed according to the National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events version 3.0. Upon occurrence of CTC grade 3 toxic events, dose reduction to 1.2 mg/kg was recommended. For all patients, staging and restaging computed tomography (CT) was obligatory. The time point of the restaging CT scans was not defined. Response was defined according to the revised response criteria for malignant lymphoma [13].

Exact confidence intervals (CIs) were used where appropriate. OS was defined as the time from the initiation of treatment with brentuximab vedotin to death from any cause and was censored at the date of last information. Progression-free survival (PFS) was defined as the time from the initiation of brentuximab vedotin to progression, relapse or death from any cause, and was censored at the date of last information on remission status. Overall survival (OS) and PFS were estimated according to the method of Kaplan and Meier, using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Patient characteristics

Fourteen patients with primary progressive or relapsed classical HL treated within the NPP without prior HDCT and autologous stem cell transplant were included in the present analysis. The baseline characteristics are presented in Table I. The median age was 45 years (range 24–74 years). At initial diagnosis, 10 patients with HL had stage III or IV disease. Primary progressive disease after first-line treatment was documented in four patients, while another four patients suffered from early and six from late relapse, respectively. The median number of prior chemotherapy regimens was 3 (range 2–6). Nine patients had not received prior HDCT and ASCT due to refractory disease; four patients were excluded from this treatment due to age and comorbidity. The reason for not performing ASCT at first relapse was unknown in one patient.

At initiation of brentuximab vedotin, eight patients with HL had stage III or IV disease, and in eight patients extranodal involvement was documented. Prior to treatment with brentuximab vedotin, 11 patients with HL had been refractory to their last chemotherapy. Except for one patient, Eastern Cooperative Oncology Group (ECOG) status was ≤ 3.

Table I. Patient characteristics.

Patient	Gender	Age	Diagnosis	Primary refractory/early relapse	Reason for no ASCT at first relapse	Clinical stage at initiation of brentuximab vedotin	ECOG	Previous chemotherapy regimens (*n*)	Refractory prior brentuximab vedotin	Time between last therapy and start of brentuximab vedotin (months)
1	Male	38	HL (NS)	No	Refractory disease	IIB	1	6	Yes	2
2	Female	29	HL (NS)	No	Unknown	IIB	1	3	Yes	1
3	Male	24	HL (LD)	Yes	Refractory disease	IVB	1	5	Yes	1
4	Male	30	HL (NS)	Yes	Refractory disease	IIB	1	3	Yes	1
5	Female	68	Comp lymphoma (HL CD30+)	Yes	Comorbidity	IIB	3	2	Yes	2
6	Female	71	HL (classic)	Yes	Refractory disease	IIIA	2	4	Yes	2
7	Male	73	HL (MC)	No	Comorbidity	IIIB	1	2	Yes	2
8	Male	36	HL (classic)	No	Refractory disease	IIB	2	2	No	22
9	Male	30	HL (classic)	No	Refractory disease	IVB	2	2	Yes	2
10	Male	52	HL (classic)	No	Refractory disease	IVB	1	5	Yes	2
11	Female	52	HL (classic)	Yes	Refractory disease	IVA	1	2	Yes	3
12	Male	72	HL (classic)	Yes	Comorbidity	IIIA	0	3	No	11
13	Male	74	HL (MC)	Yes	Comorbidity	IIA	1	2	No	10
14	Male	32	HL (classic)	Yes	Refractory disease	IVB	2	4	Yes	1

HL, Hodgkin lymphoma; NS, nodular sclerosing; LD, lymphocyte depleted; Comp, composite; MC, mixed cellularity; ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group.

The median time between last systemic therapy and initiation of brentuximab vedotin was 2 months (range 1–22).

Treatment outcome and survival rates

Patients received between 2 and 12 courses of brentuximab vedotin (median 4.5). Ten patients (71%) achieved an objective response, including five patients with CR (36%). Five patients with chemorefractory disease and all patients who did not qualify for HDCT due to age or comorbidity responded to brentuximab vedotin.

After treatment with brentuximab vedotin, five patients underwent HDCT followed by autologous or allogeneic SCT. Two patients proceeded to HDCT and autologous SCT in complete response and were in ongoing CR at the time this report was written. Two patients proceeded to HDCT and autologous SCT in progressive disease; one of them had achieved a complete response after three courses of brentuximab vedotin, and in the other patient a stable disease was documented after four courses. Both patients showed signs of progressive disease under continued treatment, and in both a complete response could be documented after HDCT and autologous SCT. One of these patients subsequently underwent reduced-intensity conditioning allogeneic SCT and died of septicemia 3 months after allogeneic SCT. In the other patient an ongoing complete response could be documented since HDCT and autologous SCT.

After achieving a complete response with brentuximab vedotin, one patient proceeded directly to reduced-intensity allogeneic SCT, but eventually developed disease progression and died of progressive lymphoma.

All patients with HL who did not receive HDCT at first relapse because of age or comorbidity achieved an objective response, including one CR and three partial responses (PRs). At the time this report was written, these patients were under continuing treatment. Details on response and courses of disease are summarized in Table II.

The median PFS for all patients included in this analysis was 9 months. With 10 of the 14 patients being alive at the time of analysis, median OS has not yet been reached. The 12-month estimate for OS was 69% (95% CI 39–100%). Kaplan–Meier curves for PFS and OS are shown in Figure 1.

Table II. Response to brentuximab vedotin and course of disease.

Patient	Best response	SCT after SGN treatment	Progression or relapse (PFS, months)	Death (OS, months)
1	CR	ASCT	No (15)	No (15)
2	CR	ASCT	No (12)	No (12)
3	CR	ASCT	Yes (7)	Yes (11)
4	PD		Yes (3)	Yes (4)
5	PR		No (5)	No (5)
6	SD		Yes (9)	No (15)
7	PR		No (1)	No (1)
8	CR	Allogeneic SCT	Yes (9)	Yes (14)
9	SD		No (2)	Yes (2)
10	SD	ASCT	Yes (3)	No (15)
11	PR		No (3)	No (3)
12	PR		No (3)	No (4)
13	CR		No (2)	No (4)
14	PR		Yes (2)	No (2)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; ASCT, autologous stem cell transplant; PFS, progression-free survival; OS, overall survival.

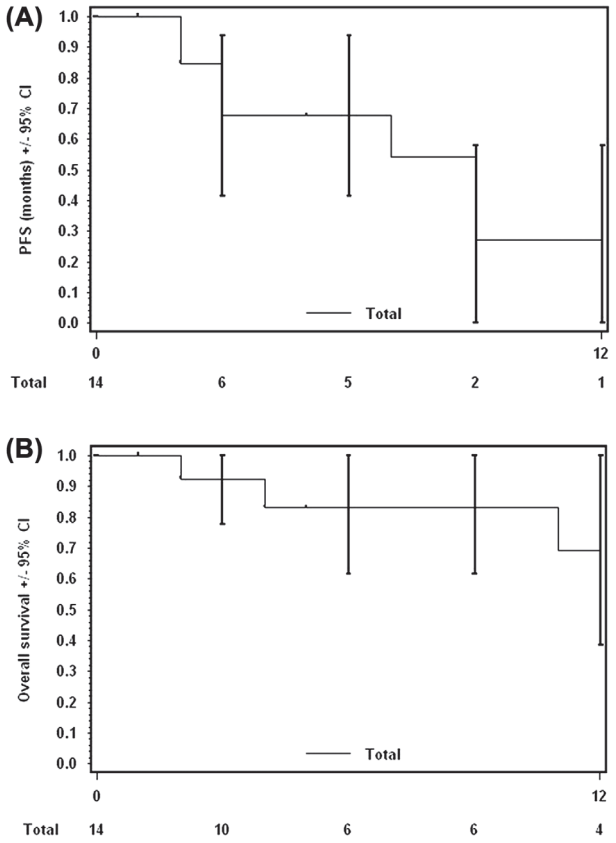

Figure 1. Kaplan–Meier plots and 95% confidence intervals for (A) PFS, (B) OS. Median PFS was 9 months, median OS has not been reached.

Toxicity

Dose reduction was not necessary, and none of the patients had to stop treatment due to toxicity. Peripheral sensory neuropathy grade 1/2 was documented in four patients; one patient developed grade 4 neuropathy after severe septicemia that was thus classified as critical illness neuropathy. Another patient had grade 2 neuropathy before starting brentuximab vedotin. During treatment, neuropathy worsened to grade 3. Severe neutropenia was observed in four patients (two grade 3, two grade 4). In two of these patients a severe infection was diagnosed and one patient had progressive HL as a possible reason for the neutropenia. Two cases of fatigue grade 2 were documented. No other grade 3/4 adverse events were documented. Noteworthy, the older patients with HL treated with brentuximab vedotin have not developed any side effects so far.

Discussion

Treatment with brentuximab vedotin resulted in an objective response in 10/14 (71%) patients with HL who were HDCT- and ASCT-naive due to refractory disease (objective responses in 5/9 patients), comorbidity (objective responses in 4/4 patients) or unknown reason (objective response in 1/1 patient).

Four patients proceeded to HDCT and ASCT, and one patient proceeded directly to HDCT and allogeneic SCT. The median PFS for all patients included in the analysis was 9 months, and the estimated 12-month OS for all patients was 69%.

The results of this retrospective analysis suggest that brentuximab vedotin is an effective salvage therapy in chemotherapy-refractory patients with HL as well as in older patients with HL who do not qualify for HDCT because of comorbidity.

So far, very limited data are available for patients who received brentuximab vedotin before HDCT and stem cell transplant. In the initial phase I trial reported by Younes *et al.*, 12 patients had not received ASCT prior to brentuximab vedotin treatment. Three of these patients responded to brentuximab vedotin, with two complete and one partial remission [14]. In a recently published retrospective analysis of 20 transplant-naive patients with HL treated with SGN-35 within two phase I trials, two complete and four partial responses were reported. Since different schedules and doses of SGN-35 were used in these trials, the results have to be regarded as preliminary in terms of efficacy [15]. Similar to our analysis, a recently published retrospective analysis of a single UK center including 12 patients with HL without prior ASCT reported a response rate of 72%, with no significant difference from those patients with prior ASCT. In accordance with our analysis, the results of Gibb *et al*. indicate that – irrespective of the previous chemotherapy approaches – brentuximab vedotin has significant activity in patients with refractory HL [16].

After achieving a response with reinduction therapy, HDCT followed by ASCT has to be regarded as the standard of care for patients with primary refractory and relapsed HL [8]. In our analysis, 4/9 patients with HL with refractory disease proceeded to HDCT and ASCT after treatment with brentuximab vedotin, and long-lasting remissions could be documented in two of these patients achieving a CR with brentuximab vedotin. Thus, brentuximab vedotin allowed proceeding to HDCT in some of those patients with chemotherapy-refractory HL, and might finally result in overcoming their dismal prognosis [8].

Since no standardized restaging schedule was recommended in the NPP, we could not assess the median number of brentuximab vedotin courses required for the best response. After an initial response to brentuximab vedotin, 2/14 patients included in our analysis developed progressive disease under continued treatment. The retrospective analysis of Gibb *et al.*, as well as data of the pivotal phase II trial, indicate that it might take not more than four courses to achieve the best response to brentuximab vedotin, suggesting evaluation of response and a decision about HDCT and autologous SCT after the fourth course of brentuximab vedotin [16].

The good anti-tumour activity and tolerability of brentuximab vedotin in patients with HL who were ineligible for HDCT due to comorbidity observed in the present analysis also suggests that this drug might be a suitable treatment option for older patients with HL. This observation is of especial clinical interest regarding the poor outcome and the limited treatment options for older patients with HL [5].

In summary, this retrospective analysis indicates that brentuximab vedotin broadens the spectrum of well-tolerated effective reinduction treatments that can be used before HDCT/ASCT in patients with primary refractory HL who might not qualify for this procedure otherwise. Our analysis also suggests that brentuximab vedotin can overcome resistance against conventional chemotherapy in refractory HL. In addition, brentuximab vedotin is also effective and well tolerated in relapsed older patients with HL, warranting further investigation in prospective clinical trials. Currently, a number of clinical trials evaluating brentuximab vedotin as single agent or in combination with chemotherapy in this setting are being initiated.

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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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